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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,672	12/09/2003	Shulamit Levenberg	0492611-0530/MIT-10077	6356

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EXAMINER	
SGAGIAS, MAGDALINE K	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
09/01/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/731,672	LEVENBERG ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-11,13-19,22-25,27-34,36-44,47-50,59-71,73 and 75-79* is/are pending in the application.

4a) Of the above claim(s) *59-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-11,13-19,22-25,27-34,36-44,47-50,71,73 and 75-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/07/2010 has been entered.

Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 59-71, 73, 75-79 are pending. Claims 6, 12, 20-21, 26, 35, 45-46, 51-58, 72 and 74 are canceled. Claims 59-70, are withdrawn. Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 71, 73 and 75-79 are under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, and 75-79 under 35 U.S.C. 103(a) as being unpatentable over Sherwood et al (Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002) in view of Griffith et al, (Science, 295: 1009-1014, 2002 (IDS)) is withdrawn in view of the declaration dated 07/07/2010 that antedates the Griffith reference.

The rejection of claims 71, 73 and 75-79 under 35 U.S.C. 103(a) as being unpatentable over Sherwood et al (Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002 (IDS)) in view of Griffith et al, (Science, 295: 1009-1014, 2002 (IDS)) and further in view of Benvenisty et al, (US 2002/0146678 (IDS)) is withdrawn in view of the declaration dated 07/07/2010 that antedates the Griffith reference.

Claims **1-5, 7-11, 13-15, 17-19, 22-25, 27-34, 36-44, 48-49, 71 and 75-79** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Sherwood et al** [Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002, IDS)] in view of **Buttery et al** [Tissue Eng, 7(1): 89-99, 2001 (IDS)]; **Athanasiou et al** [Arthroscopy, 14(7): 726-737, 1998].

Sherwood et al teaches a tissue engineering construct, comprising a porous three-dimensional cell support matrix is resistant to contractile forces exerted by chondrocytes such that a cross-sectional area of the matrix scaffolds composed of crystalline L-PLA with an inherent viscosity (I.V.) of 1.1 dl/g and 75% or 90% NaCl shrank less than 2% (abstract, p 4747, 1st column 1st paragraph and throughout the whole document) **(claims 1, 4-5, 7-11, 14-15, 23, 27-34, 38)**. Sherwood teaches a large pore size was used (>125 mm) in the bone region to further facilitate mineralized bone ingrowth and mechanical strength (P 4744, 2nd column paragraph) (porous three-diemensional cell support polymer matrix of **claim 1, 75).** Sherwood teaches the polymer of the cell support matrix comprises a 50/50 mixture of poly(L-lactic acid) and poly(Lactic acid-co-glycolic acid) (p 4744 Table 1) **(claims 11, 15, 23, 27-34, 38)**. Sherwood suggests there is a recognized and urgent need for improved treatment of articular cartilage defects (Abstract). Tissue engineering of cartilage using a cell-scaffold approach has demonstrated potential to offer an alternative and effective method for treating articular defects. Sherwood teaches a unique, heterogeneous, osteochondral scaffold using the TheriForm™

three-dimensional printing process and chondrocytes preferentially attached to the cartilage portion of the device, and biochemical and histological analyses showed that cartilage formed during a 6-week in vitro culture period. The tensile strength of the bone region was similar in magnitude to fresh cancellous human bone, suggesting that these scaffolds have desirable mechanical properties for in vivo applications, including full joint replacement (abstract). Sherwood does not specifically teach embryonic stem (ES) cells and a cell adhesion promoter and a growth factor to promote the differentiation of ES cells to form tissue-like structures.

However at the time of the instant invention **Buttery et al** teaches a tissue engineering construct comprising ES cell differentiating into osteoblasts was characterized by the formation of discrete mineralized bone nodules that consisted of 50–100 cells within an extracellular matrix of collagen-1 and osteocalcin (abstract) (embryonic stem cells of **claim 1**). Buttery teaches an extracellular matrix of collagen-1 **(**cell adhesion promoter of **claim 1**). Buttery teaches that differentiation of ES cells toward the osteoblast lineage can be enhanced by supplementing serum-containing media with ascorbic acid, β -glycerophosphate, and/or dexamethasone/retinoic acid or by co-culture with fetal murine osteoblasts (abstract) (at least one growth factor to promote differentiation of the stem cells to form tissue-like structures of **claim 1; claims 17-19, 23, 40-42, 49, 76, 78**). Buttery suggests the construct could be applied to obtain purified osteoblasts to analyze mechanisms of osteogenesis and for use of ES cells in skeletal tissue repair (abstract). Buttery teaches a growth factor of retinoic acid **(claims 77, 79)**. Buttery teaches the human ES cells **(claims 2-3, 24-25)**. Buttery teaches matrix of collagen-1 **(claims 17-19, 40-42, 65-66).** Buttery teaches the composition and concentrations of supplements described are based on conditions established for the growth and differentiation of primary osteoblast and mesenchymal stem cell cultures which embraces the cited supplements as growth factors (p 91, 1st paragraph) **(claims 19, 41-42, 44, 49, 76-79)**. Regarding the

adhesion molecule as being an integrin Buttery teaches matrix collagen-1 which embraces an integrin (**claims 13, 36**).

Buttery does not specifically teach biodegradable support matrix for the engineered construct. However, at the time of the instant invention **Athanasiou et al** [Arthroscopy, (abstract), 1998] teaches biodegradable polymers, especially those belonging to the family of polylactic acid (PLA) and polyglycolic acid (PGA), play an increasingly important role in orthopaedics (abstract). Athanasiou teaches degradation characteristics depend on several parameters including their molecular structure, crystallinity, and copolymer ratio and biomaterials such as PLA, PGA, or PLA-PGA do not denote one material, but rather a large family of materials that have a wide range of differing bioengineering properties and concomitant biological responses (abstract) (**claims 14, 37**).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some

teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Sherwood to utilizing ES-cell instead of chonrocytes, and by supplementing serum-containing media with ascorbic acid, beta-glycerophosphate, and/or dexamethasone/retinoic acid in order to enhance differentiation of ES cells toward the osteoblast lineage as taught by Buttery and using biodegradable support matrix as taught by Athanasiou with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification to use ES cells in order to produce an unlimited source of donor cells for a useful cell source for tissue engineering and repair as taught by Buttery (see abstract). This is further underscored by the teachings of Sherwood that scaffold using the TheriForm™ three-dimensional printing process showed that cartilage formed during a 6-week in vitro culture period the tensile strength of the bone region was similar in magnitude to fresh cancellous human bone, suggesting that these scaffolds have desirable mechanical properties for in vivo applications, including full joint replacement (abstract). In addition, one of skill in the art would have used biodegradable support matrix such as PLA, PGA, or PLA-PGA that have a wide range of differing bioengineering properties and concomitant biological responses in order to be fashioned into porous scaffolds or carriers of cells, extracellular matrix components, and bioactive agents as taught by Athanasiou.

Regarding the various percentages as claimed in claims 7-11, and 27-32 and that a gel coats internal and external surfaces of the cell support matrix in claims 17-19 the MPEP states that "A. Optimization Within Prior Art Conditions or Through Routine Experimentation Generally, differences in concentration or temperature will not support the patentability of

subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims **1, 16** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherwood et al [Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002, IDS)] in view of Buttery et al [Tissue Eng, 7(1): 89-99, 2001 (IDS)]; Athanasiou et al [Arthroscopy, (abstract),

1998] and further in view of **Athanasiou et al,** (39th Annual Meeting, Orthopaedic Research Society, February 15-18, 1993, p 288) thereafter referred as **Athanasiou 2**).

The teachings of Sherwood/Buttery/ Athanasiou apply here as indicated above.

Sherwood/Buttery/ Athanasiou do not specifically teach the engineered construct further comprising one or more biomolecules, small molecules, or bioactive agents disposed within the cell support matrix.

However, at the time of the instant invention **Athanasiou 2** discloses biodegradable implants using 50-50 poly(DL factide-co-glycolide) (PLG) with inherent viscocity of 0.71 d/gm combined with appropriate amount of TGFβ within the support matrix (p 288 1st column, under materials and methods). Athanasiou 2 suggests the biodegradable TGFβ matrix carrier used for cartilage healing in osteochondral defects and biodegradable carrier for delivering TGFβ in rabbit knee osteochondral defects shows that TGFβ has the ability to induce new subchondral bone hyaline neocartilage (p 288).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt

variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Sherwood/Buttery/ Athanasiou to utilizing biodegradable matrix combined with appropriate amount of TGFβ within the support matrix, such as taught by Athanasiou 2 with a reasonable expectation of success. One of ordinary skill in art would have been motivated to use biodegradable matrix combined with appropriate amount of TGFβ within the support matrix in order to regulate the differentiation of the embryonic stem cells in the support matrix into a sphere shape of condensed cells in view of the teachings of Bradham. Although Athanasiou 2 discusses regulating osteoblastic activity in chondrogenic and osteogenic sites concerning osteochondral defects in the context of healing articular cartilage, one of skill in the art would readily recognize the importance of regulating ES cell growth in the context of a scaffold for directing differentiation of ES cells to specific osteoblasts will provide a population of cells, which would provide a potentially limitless source of cells for osteochondral defects in the context of healing articular cartilage as taught by Athansiou 2.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims **1, 22, 39, 48** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherwood et al [Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002, IDS)] in view of Buttery et al [Tissue Eng, 7(1): 89-99, 2001 (IDS)]; Athanasiou et al [Arthroscopy, (abstract), 1998] and further in view of **Bradham et al** (Matrix Biol, 14(7): 561-71, 1995).

The teachings of Sherwood/Buttery/ Athanasiou apply here as indicated above.

Sherwood/Buttery/ Athanasiou do not specifically teach the engineered construct further comprising a bioactive agent.

However, at the time of the instant invention **Bradham et al** teach that reconstituted basement membrane (Matrigel) prepared from mouse Englebreth-Holm-Swarm tumor tissue was found to stimulate mesenchymal cell chondrogenesis in vitro, the production of cartilage at ectopic sites in athymic mice and the rate of chondrogenesis of mesenchymal cells from chick limb bud was increased four-fold by the addition of 400 micrograms/ml Matrigel to the media of micromass cultures (abstract) **(claim 39).** Bradham et al teach that during development of the embryonic limb, differentiation of mesenchymal progenitor cells into chondrocytes is regulated by cell shape, extracellular matrix, and growth and differentiation factors and the mesenchymal cells cultured on Matrigel, formed spheres of condensed cells (abstract) **(Claims 22, 48).**

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or

other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Sherwood/Buttery/ Athanasiou to utilizing reconstituted basement membrane (Matrigel) prepared from mouse Englebreth-Holm-Swarm tumor tissue, and, such as that taught by Bradham et al, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to use the reconstituted matrigel containing the bioactive agent prepared from mouse Englebreth-Holm-Swarm tumor tissue in order to regulate the differentiation of the embryonic stem cells in the support matrix into a sphere shape of condensed cells in view of the teachings of Bradham that the rate of chondrogenesis of mesenchymal cells from chick limb bud was increased four-fold by the addition of 400 micrograms/ml Matrigel to the media of micromass cultures.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims **1, 23, 47** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherwood et al [Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002, IDS)] in view of Buttery et al [Tissue Eng, 7(1): 89-99, 2001 (IDS)]; Athanasiou et al [Arthroscopy, (abstract), 1998] and further in view of Bradham et al (Matrix Biol, 14(7): 561-71, 1995); **Kaushall et al, (**Nat. Med, 7: 1035-1040, 2001).

The teachings of Sherwood/Buttery/Athanasiou/Bradham apply here as indicated above.

Sherwood/Buttery/Athanasiou/Bradham does not specifically teach a shear stress mechanical force.

However, at the time of the instant invention **Kaushall et al** teach that optimized preconditioning with variations of shear stress to yield the maximal retention of EPCs prior to graft implantation in vivo and promote patency in tissue-engineered (abstract), p 1036, 2nd column, 2nd paragraph). While Kaushall et al. do not specifically teach that shear stress to be used for preconditioning an engineering construct bone nodules Kaushall et al, teach that it is routine in the art to use shear stress on an engineered scaffold to increase patency of cells to the scaffold of interest. As such, because Kaushall et al, teach that shear stress and patency are functional equivalents, it would have been obvious for a patency of cells onto the support matrix. That is, it would have been a matter of design choice for an artisan to use EPCs versus a stem cell.

Claims **1, 23, 71, 43, 50, 73** are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherwood et al [Biomaterials, 23: 4739artisan to use a shear stress to promote pa–4751, 2002, Available online 10 September 2002, IDS)] in view of Buttery et al [Tissue Eng, 7(1): 89-99, 2001 (IDS)]; Athanasiou et al [Arthroscopy, (abstract), 1998] and further in view of **Benvenisty et al,** [US 2002/0146678 (IDS)]; **Kojima et al** (Experimental Cell Research, 206: 152-156, 1993 (IDS).

The teachings of Sherwood/Buttery/ Athanasiou apply here as indicated above.

Sherwood/Buttery/ Athanasiou do not specifically teach, wherein the growth factor comprises one or more of activin-A and insulin growth factor (IGF).

However, at the time the claimed invention was made, **Benvenisty et al,** teach methods for mapping a pathway of differentiation of a population of embryonic stem cells which includes exposing the cells to examples of exogenous factor include interleukins, basic fibroblast growth factor

(bFGF), transforming growth factor (TGF.beta.1), activin-A, bone morphogenic protein-4 (BMP-4), hepatocyte growth factor (HGF), epidermal growth factor (EGF), .beta. nerve growth factor (NGF) and retinoic acid (RA) for inducing differentiation of embryonic stem cells into for example into muscle-like syncytium [0040]. In addition, Bevenisty teaches culture conditions for the differentiated cell type may be any of brain cells, liver cells, pancreatic cells, muscle cells, chondrocytes, kidney cells, Mullerian duct cells, heart cells, blood cells, skin cells and adrenal cells [0015] **(claims 23, 71, 73).** Benvenisty et al, teaches the growth of human embryonic stem cells and culture of human embryoid bodies in serum-free medium with activin-A where initial differentiation of the human ES cells aggregates occurred which continued after the cells formed monolayers and when the monolayers were exposed to exogenous factors [0060]0062]. Benvenisty teaches differentiation of human embryonic stem cells to provide a uniform population of precursors and differentiated cells of a desired lineage are desirable for in vivo medical uses and for in vitro assays [0005] **(claims 43, 50).** Benvenisty et al, have also suggested it is desirable to have tools to analyze and compare pathways indifferent mammals and to combine those these tools with a methodology that permits the isolation, preservation and cultivation of embryonic stem cells from mammals for transplantation in numerous human pathologies as a component in biomedical engineering (p 1 columns 1-2). **Kojima et al** teaches that activin-A and IGF-1 are additive where activin-A augments production of IGF-1 in cultures under serum-free conditions (p 154, 2nd column).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one

known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Sherwood/Buttery/ Athanasiou to utilizing activin-A with IGF as growth factors as taught by Benvenisty/Kojima, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification since Benvenisty provides sufficient rational for one of ordinary skill in the art to apply activin-A/IGF-1 to the three-dimensional cell support system of Sherwood/Buttery/ Athanasiou exposing in order to analyze and compare pathways in different mammals and to combine those tools with a methodology that permits the isolation, preservation and cultivation of embryonic stem cells from mammals for transplantation in numerous human pathologies as a component in biomedical engineering as have suggested by Benvenisty.

Thus, the claimed invention as a whole is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, Art Unit 1632